

Targeting spin traps to mitochondria

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The mitochondrial respiratory chain is a major source of superoxide in vivo, but little is known about the nature of this radical flux, or about the biological consequences of mitochondrial radical production (1-3). To investigate the significance of mitochondrial radical production we have developed procedures to target spin traps to mitochondria. To do this we took advantage of the large membrane potential across the mitochondrial inner membrane (180 mV, negative inside). This potential gradient causes lipophilic cations, which easily pass through lipid bilayers due to their delocalised positive charge, to accumulate several hundred fold within mitochondria (1-3). In particular we have shown that by covalently linking the lipophilic alkyltriphenylphosphonium cation to bioactive molecules they can be delivered to mitochondria selectively within cells (2). Using this approach we have targeted antioxidants to mitochondria (1-3). We have now extended this approach to target the spin traps PBN and DMPO to mitochondria. This was done by covalently attaching these molecules to an alkyltriphenylphosphonium moiety. These compounds were taken up selectively by mitochondria and are accumulated several hundred fold within the mitochondrial matrix. Here we report on the development of this new class of mitochondria targeted spin trap and show how they can be used to better understand mitochondrial radical production and oxidative stress.

[1] Selective targeting of a redox-active ubiquinone to mitochondria within cells: antioxidant and antiapoptotic properties Geoffrey F. Kelso, Carolyn M. Porteous, Carolyn V. Coulter, Gillian Hughes, William K. Porteous, Elizabeth C. Ledgerwood, Robin A. J. Smith and Michael P. Murphy *Journal of Biological Chemistry* (2001) **276** 4588 - 4596

[2] Mitochondrially targeted antioxidants and thiol reagents Carolyn V. Coulter, Geoffrey Kelso, Tsu-Kung Lin, Robin A. J. Smith and Michael P. Murphy *Free Radical Biology and Medicine* (2000) **28** 1547-1554

[3] Drug delivery to mitochondria: the key to mitochondrial medicine Michael P. Murphy and Robin A. J. Smith *Advanced Drug Delivery Reviews* (2000) **41** 235-250